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| 10/616,659 | 07/09/2003 | Costas D. Maranas | P06367US03 | 9959 |

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| EXAMINER | |
|---|---|
| SKOWRONEK, KARLHEINZ R | |
| ART UNIT | PAPER NUMBER |
| 1631 | |
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/616,659 | MARANAS ET AL. | |
| | Examiner | Art Unit | |
| | Karlheinz R. Skowronek | 1631 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *31 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *6,9 and 15-17* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5, 7-8, 10-14 and 18-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Continued Examination Under 37 CFR 1.114*

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 31 October 2007 has been entered.

### *Claim Status*

Claims 1-20 are pending.

Claims 6, 9, and 15-17 stand withdrawn as being directed to a non-elected invention.

Claims 1-5, 7-8, 10-14 and 18-20 are being examined.

### *Priority*

Upon further consideration and in light of teachings in the prior art, the examiner grants priority to provisional application 60/396,763. Applicants refer to the statement in provisional application 60/396,763 at p. 3, line 7-9 which states "An MILP-based formulation for suggesting optimal gene knockouts was developed drawing upon the same duality theory concepts applied to the metabolic objective function determination formulation". In the argument presented, 31 October 2007, see remarks p. 6, Applicant states, "Such description is sufficient support and enablement to one skilled in

the art because the referenced duality theory concepts were well known to those skilled in the art".

***Claim Rejections - 35 USC § 101***

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-5, 7-8, 10-14, and 18-20 are drawn to a process and a computer based process. A statutory process must include a step of a physical transformation, or produce a useful, concrete, and tangible result (State Street Bank & Trust Co. v. Signature Financial Group Inc. CAFC 47 USPQ2d 1596 (1998), AT&T Corp. v. Excel Communications Inc. (CAFC 50 USPQ2d 1447 (1999)). The instant claims do not result in a physical transformation, thus the Examiner must determine if the instant claims include a useful, concrete, and tangible result.

In determining if the claimed subject matter produces a useful, concrete, and tangible result, the Examiner must determine each standard individually. For a claim to be "useful," the claim must produce a result that is specific, and substantial. For a claim to be "concrete," the process must have a result that is reproducible. For a claim to be "tangible," the process must produce a real world result. Furthermore, the claim must be limited only to statutory embodiments.

Claims 1-5, 7-8, 10-14, and 18-20 do not require production of a tangible result in a form that is useful to the user of the process or apparatus. The process is directed to determining candidates for gene deletion or additions using a model. While claim 19

doe recite an outputting step, the term is given its broadest reasonable interpretation based on the guidance provided in the specification. The specification does not provide guidance as to what applicant has envisioned as outputted forms. Thus, the outputting step of claim 19 has two possible interpretation, a tangible output and a non-tangible output. A tangible result requires that the claim must set forth a practical application to produce a real-world result. This rejection could be overcome by amendment of the claims to recite that a result of the process is outputted to a display, or to a user, or in a graphical format, or in a user readable format, or by including a result that is a physical transformation. The applicants are cautioned against introduction of new matter in an amendment.

***Claim Rejections - 35 USC § 112***

***Response to Arguments***

Applicant's arguments, see remarks p. 7, filed 31 October 2007, with respect to the rejection of claim 1 as lacking scope of enablement under 35 USC 112, first paragraph have been fully considered and are persuasive. The rejection of claim has been withdrawn in view of amendments made to the claim.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1, 5, 7-8, 10-11, 13-14, 19, and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hatzimanikatis et al. (IDS entry 2, 8 May 2007), in view of Bhaska et al. (Reviews in Chemical Engineering, Volume 16, Issue 1, p. 1-54, 2000), and in view of Anandalingam et al. (Annals of Operations Research, Vol. 34, p. 1-11, 1992).

The claims are drawn to a method comprising selecting a bioengineering objective function; selecting a cellular objective function forming a linear optimization problem that couples the cellular objective function with the bioengineering objective

function; and solving the linear optimization problem to yield a candidate. In some embodiments, the optimization problem includes a binary value for specifying if a flux is active or inactive. In some embodiments, the bioengineering function is over production of a chemical being directed to the relative overproduction of phenylalanine. In some embodiments, the optimization problem includes an uptake constraint. In some embodiments, the performance limits are evaluated on the ability to meet the at least objective function.

Hatzimanikatis et al. shows that objective functions can be formed for any process of interest (p. 1281, col. 2). Hatzimanikatis et al. shows improvements in the product yield, rate of production, and final product concentration are common goals in achieving more efficient and cost-effective bioprocesses (p. 1277, col. 1). Hatzimanikatis et al. shows prior research and industrial practice have clearly shown that very large increases in process performance can be realized by genetic modifications of metabolic control systems (p. 1278, col. 1). Hatzimanikatis et al. shows guidance as to what changes in regulation might be of greatest benefit to improve the network is important (p. 1278, col. 1). Hatzimanikatis et al. shows that objective functions can be formed for any process of interest (p. 1281, col. 2). Hatzimanikatis et al. shows a bioengineering objective function in eqn. 32 relating to the production phenylalanine (p.1284, col. 1). Hatzimanikatis et al. suggests that cellular growth rate can be defined as an objective function (p. 1278, col. 1). In an embodiment, Hatzimanikatis et al. shows the optimization problem includes a binary value for specifying if a flux is active or inactive (p. 1282, col. 2). In an embodiment,

Hatzimanikatis et al. show the bioengineering function is over production of a chemical being directed to the relative overproduction of phenylalanine (p.1284, col. 1). In an embodiment, Hatzimanikatis et al. shows the optimization problem includes an uptake constraint (p.1284, col. 1). the optimization problem includes a stoichiometric constraint (p. 1282, col. 1). In an embodiment, Hatzimanikatis et al. shows the performance limits are evaluated on the ability to meet the at least objective function (p. 1279, col. 1).

Hatzimanikatis et al. does not show the cellular and bioengineering objective functions that are coupled in a single optimization problem.

Bhaskar et al. shows that multiple objective optimization is applied to biochemical engineering problems such as the design of anaerobic digesters (table 1). Bhaskar et al. shows that most real world chemical engineering problems require the simultaneous optimization of several objectives (multiobjective optimization) which cannot be compared easily with each other (are non-commensurate), and so cannot be combined into a single, meaningful scalar objective function (p. 4). Bhaskar et al. shows that objective functions can be coupled through a dual problem such that the dual objective function is always bound to the original objective function called the primal (also known as bilevel)(p. 4-5). Bhaskar et al. shows that if the optimal dual objective function result is identified then the primal objective function result has also been identified (p. 5).

Anandalingam et al. shows the bilevel optimization problems described in Bhaskar et al. Anandalingam et al. shows that the decisions made by one agent, an objective function and a set of decision variables, affects the decisions made by the other agents (abstract),

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the linear programming and objective functions to predict metabolic pathway alterations of Hatzimanikatis et al. with the multiobjective optimization and dual/primal optimization problems of Bhaskar et al. because the technique of bilevel optimization and it's ability to couple objective functions was recognized as part of the ordinary capabilities of one killed in the art. One of skill in the art would have been capable of applying bilevel optimization to an optimization problem and the results would have been predictable to one of skill in the art. This is also supported by applicant's statement, "the referenced duality theory concepts were well known to those skilled in the art" (see remarks p.6, filed 31 October 2007).

Claims 1, 2, 4, and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hatzimanikatis et al. , in view of Bhaska et al., and in view of Anandalingam et al. as applied to claims 1, 5, 7-8, 10-11, 13-14, 19, and 20 above, and further in view of Yang et al.

The claims are drawn to a method comprising selecting a bioengineering objective function; selecting a cellular objective function forming a linear optimization problem that couples the cellular objective function with the bioengineering objective function; and solving the linear optimization problem to yield a candidate. In an embodiment the bioengineering objective function is lactate overproduction and acetate kinase is targeted for deletion. In an embodiment, a bioengineering objective function is

underproduction of a chemical. In an embodiment, the candidate is used to genetically modify the organism.

Hatzimanikatis et al., in view of Bhaska et al., and in view of Anandalingam et al. as applied to claims 1, 5, 7-8, 10-11, 13-14, 19, and 20 above shows a method comprising selecting a bioengineering objective function; selecting a cellular objective function forming a linear optimization problem that couples the cellular objective function with the bioengineering objective function; and solving the linear optimization problem to yield a candidate.

Hatzimanikatis et al., in view of Bhaska et al., and in view of Anandalingam et al. as applied to claims 1, 5, 7-8, 10-11, 13-14, 19, and 20 above does not show an embodiment in which the bioengineering objective function is lactate overproduction and acetate kinase is targeted for deletion.

Yang et al. shows an embodiment in which the bioengineering objective function is lactate overproduction (p. 32, col. 1) and acetate kinase is targeted for deletion (p. 27, col. 1). In an embodiment, Yang et al. shows a bioengineering objective function that is underproduction of a chemical, specifically acetate (p. 27, col. 1). In an embodiment, Yang et al. shows that the candidate is used to genetically modify the organism (p. 32, col. 1). Yang et al. shows the reduction of acetate production is of primary concern in fermentation and recombinant protein production by *E. coli* (p. 26, col. 2). Yang et al. shows that a reduction in acetate production has been shown to enhance recombinant protein production (p. 27, col. 1).

It would have been obvious to one of skill in the art to modify the method of determining gene candidates for alteration in an organism of Hatzimanikatis et al. , in view of Bhaska et al., and in view of Anandalingam et al. as applied to claims 1, 5, 7-8, 10-11, 13-14, 19, and 20 above to include the bioengineering objectives of Yang et al. because Yang et al. shows that a reduction in acetate production has been shown to enhance recombinant protein production is a primary concern in fermentation and recombinant protein production arts.

Claims 1, 5, 7-8, 10-14, and 19-20 rejected under 35 U.S.C. 103(a) as being unpatentable over Burgard et al. (Biotechnology and Bioengineering. 2001 74:364-375), in view of Bhaska et al. (Reviews in Chemical Engineering, Volume 16, Issue 1, p. 1-54, 2000), and in view of Anandalingam et al. (Annals of Operations Research, Vol. 34, p. 1-11, 1992).

The claims are drawn to a method comprising selecting a bioengineering objective function; selecting a cellular objective function forming a linear optimization problem that couples the cellular objective function with the bioengineering objective function; and solving the linear optimization problem to yield a candidate. In an embodiment the bioengineering objective function is lactate overproduction and acetate kinase is targeted for deletion. In an embodiment, a bioengineering objective function is underproduction of a chemical. In an embodiment, the candidate is used to genetically modify the organism.

Burgard et al. teach a method of identifying gene candidates for deletion and addition by forming and solving an optimization problem that involves a bioengineering objective and a cellular objective ("Mathematical modeling of gene additions/deletions", p367-369). With respect to the limitation of claim 7, drawn to a candidate deletion and a binary value specifying if a reaction is active or inactive, is also taught by Burgard et al. Burgard et al. teach the use of a binary value to specify if a reaction is active or inactive, "the binary parameter, $a_{jk}$, is defined to describe which enzymes are coded for by which genes: $a_{jk}$ = 0 if gene k has no direct effect on reaction j; 1 if gene k codes for an enzyme catalyzing reaction j ("binary parameter", p367-368, Burgard et al.). This reads on the limitation of claim, the assignment of a binary value to a reaction flux. The limitation of deletions is taught in, "In this study we explore what is the smallest gene set capable of maximizing biomass production on glucose substrate (uptake 10mmol) and what is the maximum number of gene deletions from this gene set that still maintains a specified level of biomass production (p.369)". The above statement also teaches the limitations of claim 13 drawn to the evaluation of performance limits ("smallest gene set"), the limitations of claim 20 and 14, drawn to an objective corresponding to maximizing growth rate, and the limitations of claim 5, drawn to growth ("maximizing biomass production"). The title of Burgard et al. also reads on the limitations of claim 13, performance limits. With respect to the limitations of claim 11, drawn to a chemical uptake constraint, is also taught by Burgard et al., "quantifies the network's uptake (if negative) or secretion (if positive) of metabolite i. (p. 366)" and "stoichiometric coefficient of metabolite i (p.366)". With respect to the limitation of claim 12, drawn to

quantifying the cellular objective as an aggregate flux, is also taught by Burgard et al. as "maximized the biomass production flux, $v_{max\ biomass}$. The solution yields the maximum theoretical level of biomass production ($v_{max\ biomass}$ = 1.25g biomass/gDW·h) achievable by the metabolic network within the stoichiometric constraints (p. 369)". With respect to the limitation of claim 10, drawn to at least one stoichiometric, is also taught by Burgard et al. in "These upper bounds are set by maximizing the given flux $n_j$ subject to the stoichiometric constraints (p. 369)". With respect to the limitations of claim 19 are intrinsic to the teaching of Burgard et al., "These problems are solved using CPLEX 6.6 accessed via the commercial software package GAMS. Problems with up to 3700 binary variables were solved on an IBM RS6000-270 workstation (p. 369)".

Burgard et al. do not teach the generation of a bilevel optimization problem or the coupling of cellular and biengineering objective functions.

Bhaskar et al. shows that multiple objective optimization is applied to biochemical engineering problems such as the design of anaerobic digesters (table 1). Bhaskar et al. shows that most real world chemical engineering problems require the simultaneous optimization of several objectives (multiobjective optimization) which cannot be compared easily with each other (are non-commensurate), and so cannot be combined into a single, meaningful scalar objective function (p. 4). Bhaskar et al. shows that objective functions can be coupled through a dual problem such that the dual objective function is always bound to the original objective function called the primal (also known as bilevel) (p. 4-5). Bhaskar et al. shows that if the optimal dual objective function result is identified then the primal objective function result has also been identified (p. 5).

Anandalingam et al. shows the bilevel optimization problems described in Bhaskar et al. Anandalingam et al. shows that the decisions made by one agent, an objective function and a set of decision variables, affects the decisions made by the other agents (abstract),

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the linear programming and objective functions to predict metabolic pathway alterations of Burgard et al. with the multiobjective optimization and dual/primal optimization problems of Bhaskar et al. because the technique of bilevel optimization and it's ability to couple objective functions was recognized as part of the ordinary capabilities of one killed in the art. One of skill in the art would have been capable of applying bilevel optimization to an optimization problem and the results would have been predictable to one of skill in the art. This is also supported by applicant's statement, "the referenced duality theory concepts were well known to those skilled in the art" (see remarks p.6, filed 31 October 2007).

Claims 1-4, and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Burgard et al. , in view of Bhaska et al., and in view of Anandalingam et al. as applied to claims 1, 5, 7-8, 10-11, 13-14, 19, and 20 above, and further in view of Yang et al.

The claims are drawn to a method comprising selecting a bioengineering objective function; selecting a cellular objective function forming a linear optimization problem that couples the cellular objective function with the bioengineering objective

function; and solving the linear optimization problem to yield a candidate. In an embodiment the bioengineering objective function is lactate overproduction and acetate kinase is targeted for deletion. In an embodiment, a bioengineering objective function is underproduction of a chemical. In an embodiment, a bioengineering objective function is over of a chemical. In an embodiment, the candidate is used to genetically modify the organism.

Burgard et al., in view of Bhaska et al., and in view of Anandalingam et al. as applied to claims 1, 5, 7-8, 10-11, 13-14, 19, and 20 above shows a method comprising selecting a bioengineering objective function; selecting a cellular objective function forming a linear optimization problem that couples the cellular objective function with the bioengineering objective function; and solving the linear optimization problem to yield a candidate.

Burgard et al., in view of Bhaska et al., and in view of Anandalingam et al. as applied to claims 1, 5, 7-8, 10-11, 13-14, 19, and 20 above does not show an embodiment in which the bioengineering objective function is lactate overproduction and acetate kinase is targeted for deletion.

Yang et al. shows an embodiment in which the bioengineering objective function is lactate overproduction (p. 32, col. 1) and acetate kinase is targeted for deletion (p. 27, col. 1). In an embodiment, Yang et al. shows a bioengineering objective function that is underproduction of a chemical, specifically acetate (p. 27, col. 1). In an embodiment, Yang et al. shows a bioengineering objective function that is underproduction of a chemical, specifically lactate (p. 32, col. 1). In an embodiment, Yang et al. shows that

the candidate is used to genetically modify the organism (p. 32, col. 1). Yang et al. shows the reduction of acetate production is of primary concern in fermentation and recombinant protein production by *E. coli* (p. 26, col. 2). Yang et al. shows that a reduction in acetate production has been shown to enhance recombinant protein production (p. 27, col. 1).

It would have been obvious to one of skill in the art to modify the method of determining gene candidates for alteration in an organism of Burgard et al. , in view of Bhaska et al., and in view of Anandalingam et al. as applied to claims 1, 5, 7-8, 10-11, 13-14, 19, and 20 above to include the bioengineering objectives of Yang et al. because Yang et al. shows that a reduction in acetate production has been shown to enhance recombinant protein production is a primary concern in fermentation and recombinant protein production arts.

***Response to Arguments***

Applicant's arguments, see remarks p. 8-11, filed 31 October 2007, with respect to the rejection of claims 1-5, 7-8, 10-14, and 18-20 as obvious over Burgard et al. in view of Yang et al. and in further view of Voit et al. under 35 UCS 103(a) have been fully considered and are persuasive. The rejection of claims 1-5, 7-8, 10-14, and 18-20 has been withdrawn.

***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karlheinz R. Skowronek whose telephone number is

(571) 272-9047. The examiner can normally be reached on Mon-Fri 8:00am-5:00pm (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marjorie A. Moran can be reached on (571) 272-0720. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

4 February 2008

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